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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/565,699	01/25/2006	Dieter Scheller	6102-000009/US/NP	2513
28997 7590 05/27/2010 HARNESS, DICKEY, & PIERCE, P.L.C 7700 Bonhomme, Suite 400 ST. LOUIS, MO 63105			EXAMINER CARTER, KENDRA D	
			ART UNIT	PAPER NUMBER
			1627	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/565,699	Applicant(s) SCHELLER ET AL.	
	Examiner KENDRA D. CARTER	Art Unit 1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 February 2010.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 9-82 is/are pending in the application.
- 4a) Of the above claim(s) 9,28 and 72-82 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 10-27 and 29-71 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- ☒ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>2/10/10</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The Examiner acknowledges the applicant's remarks and arguments of February 10, 2010 made to the office action filed October 23, 2009. Claims 9-82 are pending. Claims 17-20, 29-31 and 45-47 are amended. Claims 9, 28 and 72-82 are withdrawn as belonging to a non-elected group.

For the reasons in the previous office action and below, the Applicant's arguments of all 35 U.S.C. 103(a) rejections were found not persuasive, thus the rejections are upheld.

The previous 35 U.S.C. 103(a) rejections are repeated, and the Applicant's arguments are addressed below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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1) Claims 10-20, 27 and 29-71 rejected under 35 U.S.C. 103(a) as being unpatentable over Nichols et al. (US 4,501,890) in view of Pfeiffer (Drugs Aging, 2002, vol. 19, no. 8, p. 561-570), in further view of Bronzava et al. (US 2005/0038015 A1), Marquis (US 6,350,773 B1), Rimpler et al. (US 2003/0180332 A1), and Dinan et al. (US 2005/0037983 A1).

Nichols et al. teach that the compounds of Formula III and IV are dopamine D2 agonist and are substantially devoid of other agonist or antagonist blocking activities. As D2 agonsits, the compounds are useful in treating Parkinson's syndrome and depression in mammals (see abstract and column 3, lines 20-26).

Nichols et al. does not teach that rotigotine treats any type of depression (claims 10, 12-15, 32-44) in humans (claim 11) or that rotigotine is administered parenterally, trandermally or mucosally (claim 17). Nichols et al. also does not teach the amounts or rotigotine to be administered (claims 18-20 and 45-59). Nichols et al. also does not specifically teach the combination or non-combination with other pharmaceutical agents as in claims 16, 27, 29, 31, 60-71.

Pfeiffer teaches that rotigotine is a known D2 receptor agonist and is a well tolerated candidate for transdermal Parkinson's Disease treatment (see page 566, column 2, 3.3 Rotigotine, first paragraph).

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Bronzava et al. teach that D2 agonist can be combined with serotonin and/or noradrenaline reuptake inhibitory activity such as citalopram or fluoxetine (see abstract and paragraph 19).

Marquis teaches a method and composition for the treatment of depression comprising the combination of a D2/D3 agonist and an antipsychotic such as thioridazine (i.e. an anxiolytic), fluphenazine, clozapine, haloperidol, thioridazine, risperidone and olanzapine (see column 1, lines 13-20; claims 3, 6 and 10). The combination can be in a unitary form or separately for simultaneous, separate or sequential administration (see paragraph 4, lines 1-8 and lines 55-63).

Rimpler et al. teach that rotigotine (N-0923) and its metabolites and prodrugs can be administered with other agents such as diphenhydramine (see paragraphs 89, 110 and 119).

Dinan et al. teach a method of treating depression with anti-inflammatory compounds such as ibuprofen (see claim 4) in combination with antidepressant compounds (see abstract). The combination can be in a unitary dosage form or in separate dosage forms intended for simultaneous or sequential administration to a subject in need of treatment (see page 6, paragraph 68).

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Nichols et al. and the compound rotigotine to treat any type of depression in humans because of the following teachings: 1) Nichols et al. provides the teaching that D2 agonist treat depression and Parkinson's disease; 2) Pfeiffer teaches that rotigotine is a known D2 agonist and well tolerated for transdermal Parkinson's disease in humans. Thus, since it is known that D2 agonist treat both depression and Parkinson's disease, one skilled in the art would be motivated to try a known effective D2 agonist that treats Parkinson's disease to also treat any type of depression. Thus, claims 10-15, 17, 30, 32-44

In regards to the method being administered with or without another antidepressant (claims 16, 27, 29, 31, , Nichols et al. does not teach that the D2 agonist needed to be administered with another antidepressant to treat depression, thus it is understood that rotigotine would not have to be administered with another antidepressant. On the other hand, administering another anti-depressant would be obvious because both compounds would be used to treat depression. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186

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(CCPA 1960); *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992); and *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987).

In regards to the amounts of administration in claims 18-20 and 45-59, it is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

One skilled in the art would have found it obvious and motivated to administer rotigotine with the specific agents in claims 60-69 in a single or separate dose (claims 70 and 71) because Bornzava et al., Marquis, Rimpler et al. and Dinan et al. have demonstrated the combination therapy of an anti-depressant with the claimed therapeutic agents that can be administered as a single dosage form or separately. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960); *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992); and *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987).

2) Claims 23-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nichols et al. (US 4,501,890) in view of Pfeiffer (Drugs Aging, 2002, vol. 19,

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no. 8, p. 561-570), in further view of Bronzava et al. (US 2005/0038015 A1), Marquis (US 6,350,773 B1), Rimpler et al. (US 2003/0180332 A1), and Dinan et al. (US 2005/0037983 A1) as applied to claims 10-20, 27 and 29-71 above in further view of Lauterbach et al. (WO 02/089777 A1) and Hoffmann et al. (US 4,769,028).

The teachings of Nichols et al., Pfeiffer, Bronzava et al., Rimpler, and Dinan et al. are as applied above.

Nichols et al., Pfeiffer, Bronzava et al., Rimpler, and Dinan et al. do not specifically teach rotigotine in the free base or hydrochloride salt (claim 23). The above references also do not teach rotigotine in a plaster with a matrix that gives constant plasma levels (claims 24-26).

Lauterbach et al teaches rotigotine in a silicone adhesive matrix transdermal system (see page 10, lines 1-5 and 23-27) that provide sufficient drug plasma levels to provide a satisfactory therapeutic effectiveness (i.e. constant plasma level; see page 6, lines 11-20). Rotigotine is in the form of its free base (see page 11, lines 12-15), in which the final product is a film (see page 14, line 6). Transdermal equivalents of the patch are comprised in the above system (see page 10, lines 23-30).

Lauterbach et al. does not teach a plaster.

Hoffmann et al. teach a medical plaster that releases the active agent in a matrix and comprises adhesive properties (see column 3, lines 47-61 and column 5, lines 1-32) such that the release rate of the active agent may be controlled.

To one of ordinary skill in the art at the time of the invention would have found it obvious to combine the method of Nichols et al. and Pfeiffer and rotigotine free base (claim 23) in a plaster with a matrix that gives constant plasma levels (claims 24-26) because of the following teachings: 1) Lauterbach et al. teach a film of rotigotine in a silicone adhesive matrix transdermal system (see page 10, lines 1-5 and 23-27) that provide sufficient drug plasma levels to provide a satisfactory therapeutic effectiveness (i.e. constant plasma level; see page 6, lines 11-20); and Hoffmann et al. provides teaching that adhesive medical plasters can be made to provide controlled release of active agents. Thus, one skilled in the art can make a plaster of the Lauterbach et al. transdermal system to provide controlled release of the rotigotine.

3) Claims 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nichols et al. (US 4,501,890) in view of Pfeiffer (Drugs Aging, 2002, vol. 19, no. 8, p. 561-570), in further view of Bronzava et al. (US 2005/0038015 A1), Marquis (US 6,350,773 B1), Rimpler et al. (US 2003/0180332 A1), and Dinan et al. (US 2005/0037983 A1) as applied to claims 10-20, 27 and 29-71 above in further view of den Daas et al. (Naunyn-Schmiedeberg's Arch Pharmacol, 1990, 342, pp. 655-659).

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The teachings of Nichols et al., Pfeiffer, Bronzava et al., Rimpler, and Dinan et al. are as applied above.

Nichols et al., Pfeiffer, Bronzava et al., Rimpler, and Dinan et al. do not specifically teach a prodrug of rotigotine as in claims 21 and 22.

Den Daas et al. teach that prodrugs of rotigotine (i.e. N-0437), including the acetyl, propionyl and the isobutyryl ester give activity after 2-3 hours after application and provides activity after 23 hours (see page 656, column 2, last paragraph), compared to the transdermal application of rotigotine. Possible reasons for the lag time difference for transdermal application between rotigotine and its prodrugs is that the limited amount of metabolizing enzymes in the skin first inactivate N-0437, and that subsequently the remaining free N-0437 can penetrate the circulatory system. The ester prodrugs are protected against metabolic attack in the skin and enter more rapidly (see page 658, column 2, paragraph 2).

To one of ordinary skill in the art at the time of the invention would have found it obvious to combine the method of Nichols et al. and Pfeiffer and a prodrug of rotigotine as in claims 21 and 22 because den Daas et al. teach that prodrugs of rotigotine are active before rotigotine transdermally because the ester prodrugs are protected against metabolic attack in the skin and enter more rapidly (see page 658, column 2, paragraph 2).

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive.

The Applicant's argue that there is no motivation to combine the six cited documents because none of the documents teach that rotigotine is utilized in the treatment of depression. The compounds of Nichols are not similar to rotigotine, and the fact that they are both D₂ agonist is not enough to establish that rotigotine will effectively treat depression. Only with hindsight would one know that rotigotine has antidepressant properties. Further, no reasonable expectation of success that rotigotine or salts thereof could treat depression based on an "obvious to try" standard. Moreover, one would not combine another anti-depressant under *In re Kerkoven* because rotigotine is not a known antidepressant. The same arguments hold true for the eight way rejection over Nichols, Pfeiffer, Bronzava, Marquis, Rimpler, Dinan, Lauterbach and Hoffman, and the seven way rejection over Nichols, Pfeiffer, Bronzava, Marquis, Rimpler, Dinan and den Daas. Regarding den Das, four of the ester prodrugs were not active and he does not disclose, teach or suggest carbamate, carbonate, ketal, acetate, phosphate, phosphonate, sulfate or sulfonate prodrugs.

The Examiner disagrees because motivation to combine the references have been given in the previous office action and above. Particularly, there is an obviousness to try and expectation of success for rotigotine to have anti-depressive activity because the compound of Nichols and rotigotine are both D₂ agonist and treat Parkinson's disease. Thus, the method of treating depression and Parkinson's disease is effective through the D₂ agonistic pathway. One skilled in the art would obviously try rotigotine for depression because of its mechanistic action and common therapeutic efficacy for Parkinson's disease as the Nichols compounds. Those, compounds of this

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type would obviously be combined together and with other anti-depressant compounds in order to effectively treat depression and Parkinson's disease.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to den Das, the claims include that ester prodrugs can be used, in which den Das teach that prodrugs of rotigotine (i.e. N-0437), including the acetyl, propionyl and the isobutyryl ester give activity after 2-3 hours after application and provides activity after 23 hours (see page 656, column 2, last paragraph), compared to the transdermal application of rotigotine. Thus, one would be motivated to use the ester prodrugs of rotigotine for the above reasons and further because the ester prodrugs are protected against metabolic attack in the skin and enter more rapidly (see page 658, column 2, paragraph 2). Den Das does not need to teach the other claimed prodrugs because the ester prodrugs are taught and thus teaching the limitations of claims 21 and 22.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KENDRA D. CARTER whose telephone number is (571)272-9034. The examiner can normally be reached on 9:00 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone

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number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kendra D Carter/
Examiner, Art Unit 1627

/Shengjun Wang/
Primary Examiner, Art Unit 1627